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### **A 59 year old man with progressive spinal cord and peripheral nerve dysfunction culminating in encephalopathy**

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## CLINICOPATHOLOGICAL CASE CONFERENCE

## A 59 year old man with progressive spinal cord and peripheral nerve dysfunction culminating in encephalopathy: Edinburgh advanced clinical neurology course, 1999

R Al-Shahi, C P Warlow, G H Jansen, CJM Frijns, J van Gijn

### Case presentation

A 59 year old, retired metal worker presented with a 3 month history of difficulty walking. He had initially developed left leg weakness, followed 1 month later by numbness of both legs, a burning sensation in his anal region and penis, constipation, urinary frequency, retention, and incontinence. At that stage he presented to another hospital with abdominal pain, but all investigations for this were normal. On examination there was some weakness of his left leg, but no objective sensory loss in the legs or perineum. The weakness progressed to involve his right leg over the next 2 months such that he needed a stick to walk.

For 6 years before presentation he had had unremitting paraesthesiae of both shins, for which no cause had been found. He had been judged unfit to work 4 years previously due to depression. Ankylosing spondylitis had been diagnosed at the age of 30, followed by proctitis 10 years later for which he had been successfully treated with sulphasalazine.

Cognitive, cranial nerve, cerebellar, and general physical examination were unremarkable. Upper arm and pectoralis muscles were atrophied, but not weak. His gait was broad based, stiff, and he dragged both feet. There was bilateral MRC grade 4 weakness of knee flexion and MRC grade 4+ weakness of the left extensor hallucis longus muscle. Jaw jerk was absent, but deep tendon reflexes in the arms and legs were brisk with clonus at the right ankle, an absent left ankle jerk, and up going plantar responses. Pain and touch sensations were diminished over both forearms, as they were below both knees with additional impairment of vibration sense.

Initial abnormal investigations were C reactive protein 43.7 mg/l (reference range (RR) 0-8 mg/l), lactate dehydrogenase 638  $\mu\text{mol/l}$  (RR 300-620  $\mu\text{mol/l}$ ), serum angiotensin converting enzyme (SACE) 28 U/l (RR 8-21 U/l) rising to 36 U/l two months after presentation, and protein electrophoresis showed two paraproteins, one band of IgG- $\kappa$  and three bands of IgM- $\lambda$ . There were occasional leucocytes (never more than 20 per high power field) and some erythrocytes in the urine. Autoantibody

screen, erythrocyte sedimentation rate, HIV and Lyme serology, tuberculin test, and the rest of the serum biochemistry and urine examination were normal. Examination of the CSF on three occasions demonstrated a maximal protein of 1.25 g/l, maximal white cell count of  $13 \times 10^6/\text{l}$ , IgG index of 0.50 (normal <0.60), no growth from bacteriological cultures, and unremarkable cytology and serology.

Magnetic resonance imaging of the lumbar spine was initially normal, but on two subsequent examinations, within a month of presentation, a small contrast enhancing lesion was seen adjacent to a spinal root in the vicinity of the medullary conus (fig 1). Brain MRI soon after presentation showed small, scattered lesions in the subcortical and periventricular white matter (fig 2), with a larger lesion in the right frontal lobe (fig 3); these appearances were unchanged 3 months later. Initial EMG showed denervation in the left gastrocnemius and biceps femoris muscles. Nerve conduction studies revealed normal velocities, action potential amplitudes, F responses, and H reflexes in motor and sensory nerves. The following studies were consistently normal: MR imaging of the cervical and thoracic cord, MR angiography of the whole cord, cerebral and spinal catheter angiography, chest radiography, skeletal survey, CT of the thorax, ultrasound and CT of the abdomen, sensory, motor (magnetic stimulation) and visual evoked potentials, skin biopsy, liver biopsy and bone marrow examination.

Over the next 3 months he developed increasingly painful dysaesthesia and sensory loss over his hands and feet. Due to this deterioration he became increasingly dependent on others and was unable to walk. Visual acuity deteriorated to 6/7.5 on the right and 6/12 on the left, with photophobia, but no eye pain; an ophthalmologist diagnosed anterior uveitis and found a few small, peripheral retinal haemorrhages. Livedo reticularis appeared over his legs. At this stage he was treated with 75 mg per day oral prednisolone, increasing to 100 mg per day after 2 weeks, and gradually tapered off over subsequent weeks without any clinical improvement.

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Figure 1 MR imaging of the lumbosacral spine (T1 weighted, sagittal section) with gadolinium contrast showing a small, enhancing area in the vicinity of the medullary conus (arrow).

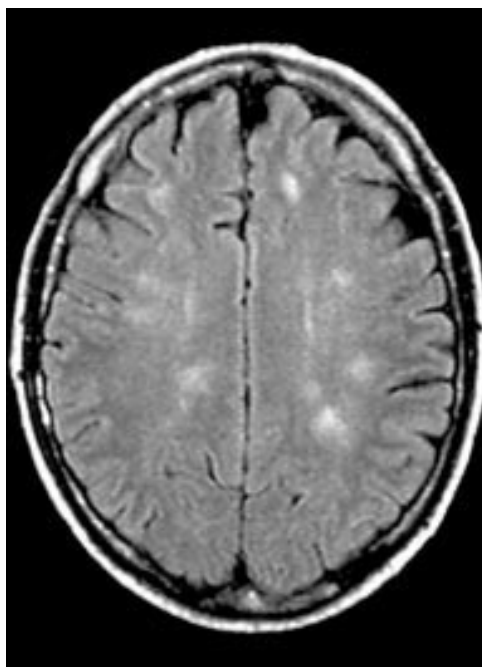


Figure 2 Brain MRI (FLAIR, axial section) showing scattered lesions in the subcortical and periventricular white matter.

Four months after presentation he had a generalised epileptic seizure which was complicated by aspiration pneumonia requiring short term mechanical ventilation. There was diffuse slow wave activity on an EEG, with no abnormal discharges. At that time his leg weakness and muscle wasting progressed rapidly and a follow up EMG showed denervation in all muscles studied, affecting the legs more than

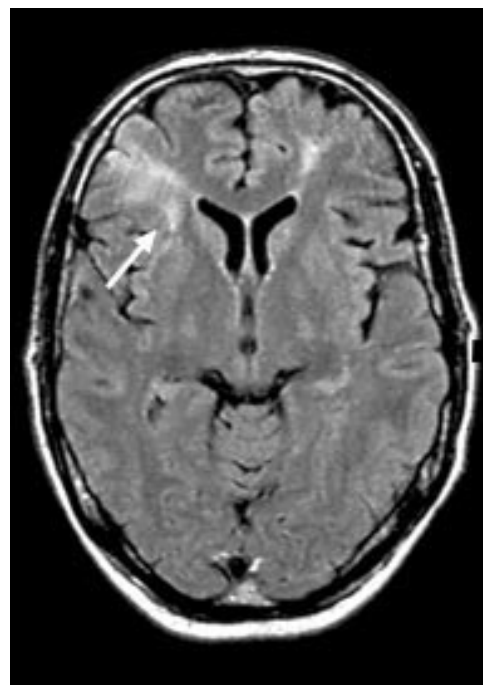


Figure 3 Brain MRI (FLAIR, axial section) showing a lesion involving the grey and white matter of the right frontal lobe (arrow).

the arms and distal more than proximal muscles. Repeated nerve conduction studies were abnormal in all nerves tested: action potential amplitude was decreased in the motor (CMAP 2 mV) and sensory (SNAP 3  $\mu$ V) fibres of the right median nerve, from which distal sensory conduction velocity was 46 m/s and motor conduction velocity was 48 m/s; there were no responses from the motor fibres of the right peroneal nerve, the sensory fibres of either sural nerve, nor the right ulnar and radial nerves. He became intermittently psychotic. After another bout of aspiration pneumonia he developed pulmonary embolism. He died after another seizure, despite phenytoin treatment, 9 months after the beginning of his illness. Sixteen days before his death an investigation had been performed which suggested the diagnosis. A postmortem examination was performed.

## Discussion

### CLINICAL FEATURES

#### Professor Charles Warlow

This 59 year old man's final neurological illness started with progressive problems affecting his legs and sphincters, immediately suggesting a disorder of the spinal cord or cauda equina. The first proper neurological examination was normal above the neck, but there were definite upper motor neuron signs in the legs—judged by an expert on the Babinski sign in Utrecht.<sup>1</sup> Sensory loss below the knees and an absent left ankle jerk suggested an additional spinal root problem. However, the sensory loss could have been due to a cord lesion, so root or peripheral nerve involvement was not definite. Rather unexpectedly, there were upper limb signs including brisk tendon jerks and “muscle atrophy” without weakness. But, on the whole, if

there is no weakness, then wasting should not be used to localise a neurological lesion. So at presentation this may not just have been a lower spinal cord syndrome; there may have been cervical cord pathology too. I shall come back to the 5 year history of persisting pins and needles in both shins.

In anyone with a deteriorating spinal cord syndrome and upper limb signs, if not symptoms, an MR scan of the whole cord is needed. MR scans (without contrast, frustratingly) of the cervical, thoracic, and lumbar spine were initially normal, apart from the typical changes of ankylosing spondylitis. Two months after initial presentation, however, a repeat MR of the lumbar cord disclosed, with gadolinium enhancement, a small enhancing lesion seemingly attached to the meninges, either at the conus, or on a spinal root (fig 1). This could have been a tumour, granuloma, or an infiltrative lesion. Inexplicably, a brain MR had been performed *before* the lumbar spinal MR, notwithstanding the lack of any problem above the neck. Surprisingly, the scan was very abnormal indeed (figs 2 and 3). The lesion in the grey and white matter of the right frontal lobe could have been an infarct or tumour, but there was no mass effect in favour of a turnover; the scattered lesions were clearly abnormal and did not look like multiple sclerosis, progressive multifocal leukoencephalopathy, acute disseminated encephalomyelopathy or small vessel disease, mostly because some of the lesions were in cortical grey matter.

Given the more or less normal spinal imaging, the CSF was examined, very sensibly not just once but three times, disclosing a very mild lymphocytic pleocytosis with normal cytology and a slightly raised protein, but no evidence of intrathecal immunoglobulin production. Initial electrophysiological tests showed denervation in the leg muscles innervated just by the left L5 and S1 roots; only much later did they demonstrate denervation in the arm muscles as well, and impaired motor and sensory conduction in the upper and lower limbs suggesting not so much a generalised neuropathy as mononeuritis multiplex.

After 3 months the patient was going from bad to worse with definite motor and sensory dysfunction in the upper as well as the lower limbs. Further to the raised lactate dehydrogenase and C reactive protein and paraproteinaemia, a systemic disorder was suggested by livedo reticularis, uveitis, and retinal haemorrhages. But skin, liver, and bone marrow biopsies were all frustratingly normal. A generalised epileptic fit heralded a further decline, despite corticosteroid treatment, and focused minds on the brain because an EEG was done the next day and showed diffuse abnormalities consistent with a global encephalopathy. Further imaging of the brain was unhelpful but "another procedure" was performed which suggested the diagnosis 16 days before his death.

Asking the first question in neurological diagnosis, "where is the lesion?" it is clear that this patient did not have one focal lesion, but a multifocal or diffuse pathological process,

affecting his brain, spinal cord, nerve roots, and peripheral nerves too. Answering the second question, "what is the lesion?" is much more difficult because the multitude of abnormalities suggests a range of possibilities. His age puts neoplasia high on the list, the rate of progression again suggests neoplasia or chronic inflammation, and there were very important hints at a systemic illness (paraproteinaemia, raised SACE, acute phase response, livedo reticularis, haematuria, retinal haemorrhages, and uveitis), let alone the ankylosing spondylitis and inflammatory bowel disease.

Taking the systemic clues one at a time, the only neurological complication attributable to ankylosing spondylitis is a cauda equina syndrome, but the patient had far more than that.<sup>2</sup> There are numerous neurological complications of and associations with inflammatory bowel disease (suggested by the patient's proctitis) but they are all very rare, especially with quiescent disease.<sup>3</sup> I do not think that the sulphasalazine was responsible, although it can very rarely cause neurological disorders (dissimilar to this patient's syndrome) that are said to occur shortly after starting the drug.<sup>4</sup>

A mildly raised C reactive protein is very non-specific, but it does suggest some sort of underlying systemic inflammation, although the spondylitis or proctitis could have been responsible for this. A malignancy or chronic infection cannot be excluded by a normal erythrocyte sedimentation rate, nor can they be implicated by a mildly raised lactate dehydrogenase. I think that the haematuria was probably insignificant in the absence of urinary casts and renal dysfunction. A raised SACE is neither a sensitive nor a specific test for sarcoid.<sup>5</sup> Even though the patient was some sort of metal worker, I do not think that this is relevant. Too much reliance should not be placed on the negative tuberculin test as sarcoid, lymphoma, and any serious illness, including tuberculosis itself and monoclonal gammopathy, can all suppress cell mediated immunity. The biclonal paraproteinaemia could be attributed to a very rare biclonal myeloma, but the bone marrow was normal (we are not told whether this was by trephine, which would have been more likely than just an aspirate to pick up any abnormality) and there was no bone pain, nor lesions on skeletal survey, anaemia, renal failure, raised erythrocyte sedimentation rate, hypercalcaemia, or Bence-Jones proteinuria. Many of the other causes of paraproteinaemia can be rejected, but

#### **Box 1: Causes of paraproteinaemia**

Multiple myeloma/solitary plasmacytoma  
Waldenström's macroglobulinaemia  
Monoclonal gammopathy of undetermined significance (MGUS)  
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin lesions)  
Primary amyloidosis  
B cell lymphomas  
Chronic lymphocytic leukaemia  
Mixed essential cryoglobulinaemia



I will come back to amyloid, lymphoma, and mixed essential cryoglobulinaemia (box 1).

Livedo reticularis has a wide differential diagnosis (box 2), and in the context of this case vasculitides, intravascular obstruction, and lymphoma need to be considered. I guess it was the livedo that led to the skin biopsy, but that was reported as normal. The patient's two ophthalmological problems were far from specific. We are told that the uveitis was anterior, but there was no pain, watering, or reddening, so maybe this was really posterior uveitis rather than iridocyclitis. Regardless, the uveitis may be attributable to the spondylitis or proctitis but among the many other causes of uveitis I will return to sarcoid (suggested by raised SACE), a chronic infection perhaps, malignancy, and vasculitis. Retinal haemorrhages also occur in many of the things we may be interested in, including vasculitis. So the eyes are not a lot of help except to confirm that we must be dealing with a systemic and not just a neurological disease.

I do not think that this illness was due to some sort of mycobacterial or fungal chronic infection as the clinical picture and investigations were not consistent with such a diagnosis; furthermore, the paraproteinaemia and longstanding paraesthesiae, if relevant, would remain unexplained. Cancer has to be considered because the systemic disease was progressive and killed the patient in 9 months. I do not think the cerebral lesions were metastases because they were the wrong shape, there was no mass effect, and they did not grow. Nor does malignant meningitis fit, although the enhancing cord lesion could have been a meningeal metastasis. There were none of the clinical features of chronic meningitis, the CSF was not particularly abnormal, and the glucose was normal. The CSF cytology was normal although it can remain so in malignant meningitis even after several lumbar punctures, and also he survived too long without treatment for malignant meningitis. Nor are we dealing with a paraneoplastic syndrome because there was no evidence of a primary tumour, the cerebral MR changes were so pronounced, the spinal lesion on MR would remain unexplained, and

### Box 2: Causes of acquired livedo reticularis

Vessel wall disease:

*Vasculitis, atherosclerosis*

Intravascular obstruction:

*Hypercoagulability, paraproteinaemia, cryoglobulinaemia, cholesterol embolisation syndrome, disseminated intravascular coagulation, decompression sickness*

Infections:

*Tuberculosis, meningococcus, endocarditis, syphilis, typhus fever*

Drugs:

*Amantadine, quinine, catecholamines*

Metabolic/endocrine:

*Cushing's disease, hypothyroidism, pellagra*

Miscellaneous:

*Cardiac failure, lymphoma, oxalosis, acute pancreatitis*

### Box 3: Neurological complications of sarcoidosis

Chronic meningitis±cranial neuropathies

Brain and meningeal granulomata

Infiltration of the optic nerve/orbit/chiasm

Spinal cord/root granulomata

Sarcoid angiitis of the brain/spinal cord

Mononeuropathy, mononeuritis multiplex, polyneuropathy

Muscle granulomata

Opportunistic infections

CSF may have mildly raised lymphocytes, protein and immunoglobulin synthesis, and a slightly low glucose

any neuropathy is usually distal, symmetric, and sensory. And, of course, the livedo reticularis and paraproteinaemia would have to be explained. Primary amyloidosis is worth considering because of its association with a paraproteinaemia, but its neurological complications are dissimilar to this case (diffuse peripheral neuropathy with a strong autonomic component is the most common manifestation, while entrapment neuropathies, myopathy and cranial neuropathies are very rare) and none of its systemic complications were present.

### DIFFERENTIAL DIAGNOSIS

There are three possibilities that must surely include the diagnosis. Lymphoma is a candidate in the face of a widespread and obscure neurological disorder with uveitis and a paraprotein (which can appear with, or long before, lymphomas of the B cell type). I do not think, however, that either a systemic or primary CNS lymphoma is the cause. There are absolutely no cerebral or spinal masses apart from the very small spinal lesion, and the meningitis is not at all likely to be malignant with a 9 month survival. Moreover, primary CNS lymphoma would not explain the mononeuritis multiplex and livedo reticularis.<sup>6</sup>

The second possibility is sarcoidosis in view of the cerebral infarcts, or perhaps granulomatous changes on the brain MR, spinal cord involvement, root and peripheral nerve signs, uveitis, and raised SACE (box 3). The CSF was compatible. Knowing the CSF ACE, which is neither a specific nor sensitive test, would not have helped.<sup>5</sup> But, many features were not consistent with sarcoid, including the patient's age, normal liver and skin biopsies, lack of response to steroids, and the relentlessly progressive clinical course. Nor are paraproteins or livedo reticularis found with sarcoid.

The third possibility is one of the myriad of vasculitides, suggested by such a diffuse disease of the nervous system, what look like infarcts on the brain MR, livedo reticularis, and the exclusion of more or less everything else in the differential. I do not think that it was a systemic necrotising vasculitis such as microscopic polyangiitis or polyarteritis nodosa because the relevant antibodies were negative, there was no renal impairment, and the erythrocyte sedimentation rate was normal.<sup>7</sup> Nor do I think it was isolated angiitis of the CNS, because this

does not affect peripheral nerves, and there should not be so many systemic features such as the livedo reticularis, uveitis, retinal haemorrhages and raised C reactive protein.<sup>8</sup> Clearly the vasculitides associated with Behçet's disease, rheumatoid arthritis, Sjögren's syndrome, relapsing polychondritis, systemic sclerosis, and malignant atrophic papulosis do not fit because there were none of their specific features. The clinical picture was wrong for giant cell arteritis and Takayasu's disease. The cholesterol embolisation syndrome can masquerade as systemic vasculitis with livedo reticularis, but the electrolyte sedimentation rate was not raised and there was no suggestion of widespread and severe atheroma.<sup>9</sup> I do not think that this man had systemic lupus erythematosus because he was the wrong age and sex, the only other organs affected were the skin and eyes, antinuclear antibodies were negative, and the C reactive protein should not have been raised. I wonder why the results of the antiphospholipid antibody level and the lupus anticoagulant assay were not given, or any indication that transoesophageal echocardiography was done looking for mitral valve vegetations. Was this the late breaking thought and so the diagnostic test that suggested the diagnosis? Although the livedo reticularis is suggestive of the antiphospholipid antibody syndrome, as are the ischaemic looking lesions on brain MR, spinal cord involvement is almost unheard of and the peripheral nerves are never involved.<sup>10</sup> Turning to the paraproteins, the only vasculitis I know to be associated with a serum paraprotein is mixed essential cryoglobulinaemia. This disease is a systemic vasculitis affecting arteries and veins, in the presence of a circulating cryoglobulin. Many of the systemic features of mixed essential cryoglobulinaemia were not present, and its principal neurological complications are an axonal peripheral neuropathy or mononeuritis multiplex.<sup>11</sup> I have found only two case reports of a subacute encephalopathy caused by occlusion of small cerebral vessels, thought to be due to the precipitation of cryoglobulins,<sup>12 13</sup> but in the presence of obvious systemic illness, unlike our case. Any spinal cord involvement is, I think, unheard of, the disease tends to be more chronic than what we are dealing with here and, finally, the paraprotein is normally a single monoclonal IgG with a polyclonal response, not biclonal.

The only other possible diagnosis in my mind is intravascular lymphoma. It is exceedingly rare and so perfect for a clinicopathological conference.<sup>14-16</sup> The neurological features (box 4) are probably all due to vascular plugging by malignant lymphoma cells.<sup>17 18</sup> The features that would seem to fit with this diagnosis are widespread neurological involvement in the presence of a non-specific CSF, rapid progression to death, normal bone marrow and liver biopsies, uveitis, and retinal haemorrhages. Livedo reticularis, paraproteinaemia, and raised SACE have all been described and the normal erythrocyte sedimentation rate and raised C reactive protein do not

#### **Box 4: Neurological features of intravascular lymphoma<sup>18</sup>**

Multifocal cerebral infarcts causing stroke-like episodes and a chronic or subacute encephalopathy (rarely transient ischaemic attacks)

Spinal cord syndrome with pain

Peripheral/cranial neuropathy and radiculopathy

Raised CSF protein with lymphocytic pleocytosis

Non-specific beading and dilatations on cerebral arteries seen on angiography

exclude the diagnosis. The lactate dehydrogenase and erythrocyte sedimentation rate are usually higher, but they do not have to be. The patient's early abdominal pain may have been attributable to mesenteric ischaemia and his longstanding paraesthesiae caused by paraproteinaemia (which might have been regarded as a benign gammopathy in the early stages). The normal skin biopsy would seem to be inconsistent, but this may have missed the patchy vascular lesions. The small, enhancing lesion near the cauda equina could have been an extravascular deposit. I am troubled by the lack of progression of the MR changes and if the frontal lesion (fig 3) was an infarct due to intravascular lymphoma, it is odd that no atrophy developed around it with enlargement of the frontal horn.

To achieve a diagnosis during life, short of sitting down quietly, taking the history again from scratch, re-examining the patient, and looking at all the investigations yet again, I would have done a brain biopsy. I think that such a biopsy would have shown intravascular lymphoma.

#### **Questions**

*Professor Jan van Gijn*

"Would you put a number to your degree of certainty about intravascular lymphoma as the primary diagnosis?"

*Professor Charles Warlow*

"Yes, 100%."

*Member of the audience*

"Why would you not have done a sural nerve biopsy?"

*Professor Charles Warlow*

"I would have been thinking of lymphoma or vasculitis so, in the presence of three normal biopsies elsewhere, I would have gone straight for the right frontal lesion, to get a sample of meninges and cortex, in other words something that was so obviously affected."

*Dr Geraint Fuller*

"Why not biopsy the lesion near the conus?"

*Professor Charles Warlow*

"I think that might have been technically difficult. What does a neurosurgeon think?"

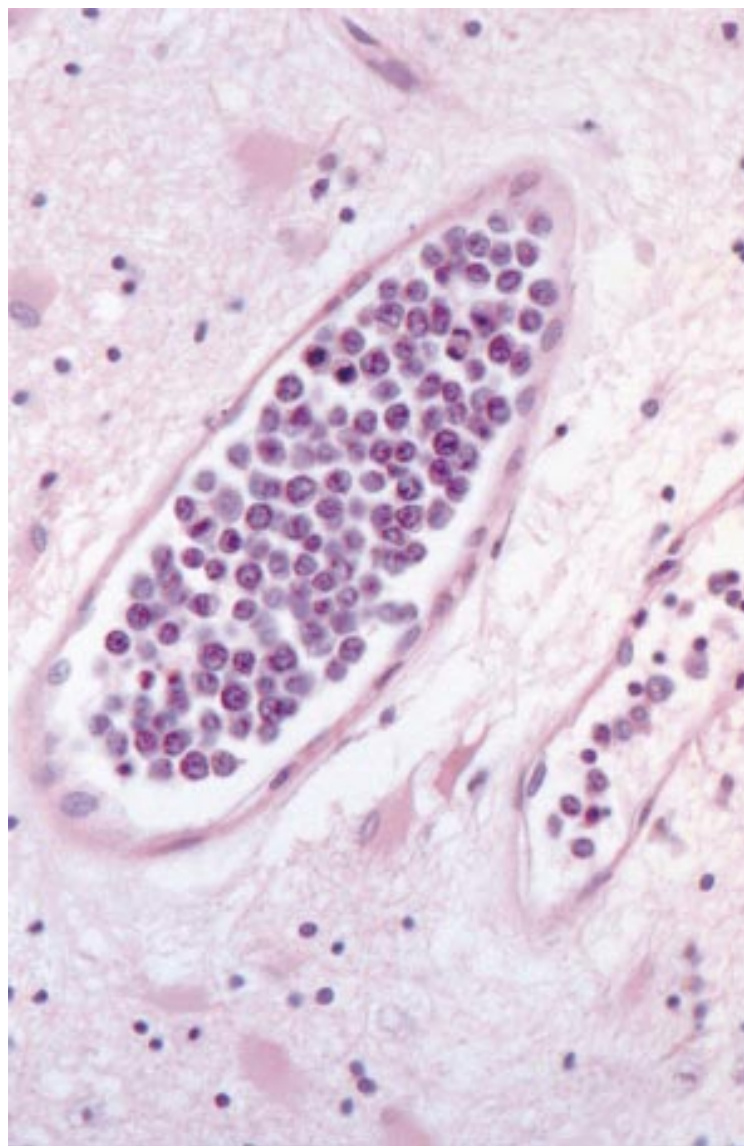


Figure 4 Intracortical vein showing atypical lymphoid cells with mitosis (haematoxylin and eosin, magnification×100).

*Mr John Garfield*

"It might be possible, but I, like you, would biopsy the pathology in the brain."

*Professor Jan van Gijn*

"Where would a muscle expert have directed his investigations, in view of the electrophysiology?"

*Dr David Hilton-Jones*

"You want me to say biopsy muscle, of course! Biopsying asymptomatic muscle is not highly productive. If the sural nerve neurophysiology was abnormal, I think that would not be an unreasonable place to look."

*Member of the audience*

"I wonder if the patient's illness could have been related to spinal irradiation in the past as treatment for ankylosing spondylitis?"

*Professor Charles Warlow*

"I don't think that would be consistent with such a rampant 9 month history, or the brain involvement."

*Professor Michael Harrison*

"Was it true that there was no enhancement on the cranial MR?"

*Professor Charles Warlow*

"Contrast was not administered with his cranial MR—a major omission!"

*Professor Jan van Gijn*

"Ian, what are your thoughts?"

*Professor Ian McDonald*

"John Garfield and I were just saying to each other that we have not even heard of a number of these conditions! As one of Charles' teachers, I got as far as lymphoma, but I did not know about intravascular lymphoma, although I am persuaded by this."

*Professor Jan van Gijn*

"Michael Donaghy, what did you think?"

*Dr Michael Donaghy*

"Well it is now clear to me that it must have been one of: sarcoidosis, intravascular lymphoma or vasculitis! I think the livedo reticularis puts one off sarcoid, but I am persuaded by Charles' diagnosis."

*Dr Jan van Gijn*

"Could we have the last word from Newcastle?"

*Dr David Bates*

"I must be slightly disingenuous because I thought this was a B cell lymphoma, but I am attracted by the concept of this being intravascular lymphoma, although I am worried slightly by the lack of change in the MR scan over the 3 months."

## Pathology

*Dr Gerard Jansen*

At postmortem the heart, liver, and kidneys were normal. The spleen was enlarged and softened, and several petechial haemorrhages were present in the mucosa of the stomach. The lungs were congested with four small hemorrhagic infarcts due to pulmonary emboli.

External examination of the brain, which weighed 1550 g, was normal. Internal examination showed small patches of discolouration and softening of the right frontal cortex and the left precentral gyrus. The brain stem, cerebellum, and spinal cord were macroscopically normal. On microscopy of the frontal cortical ribbon there was widespread gliosis and a small infarct. Similar appearances were scattered throughout the brain. There was demyelination of the white matter and occasional macrophages, which led me to examine the blood vessels further. Whole vessels in the white matter were completely clogged with mitotic, rounded cells (fig 4), which were also found in other organs. These neoplastic cells were CD-20 and CD-79a positive, and expressed  $\kappa$  light chains (fig 5), but not heavy chain immunoglobulins. There were no CD-3 or other T



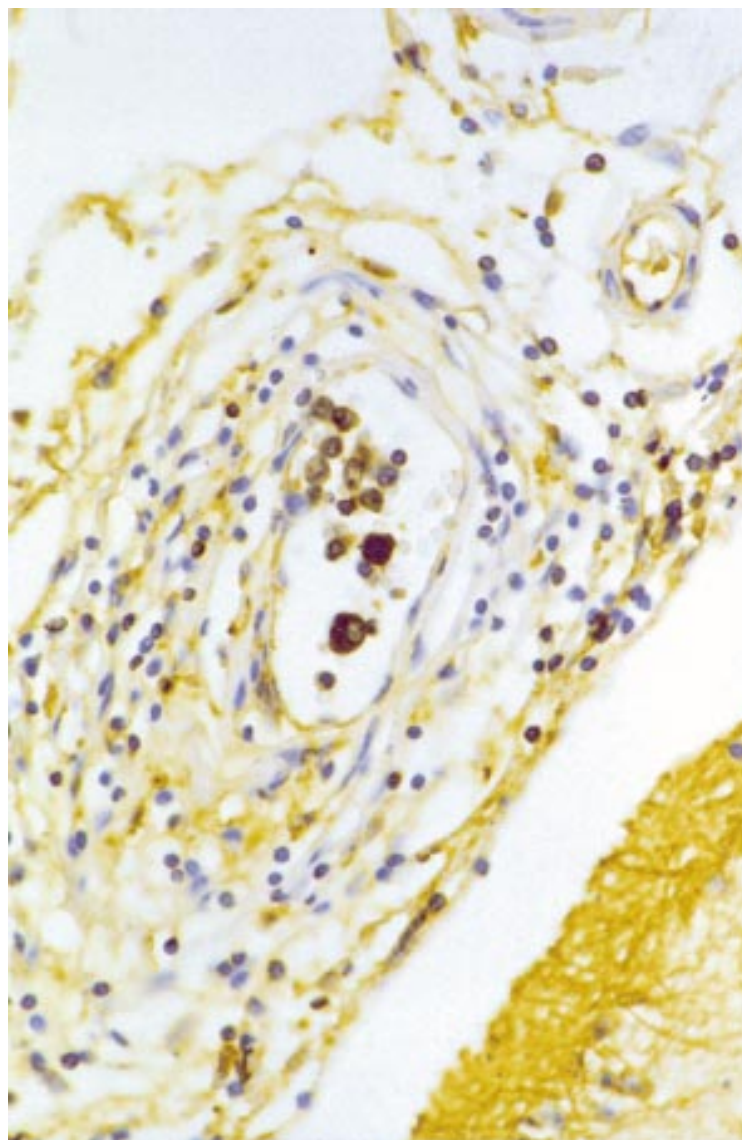


Figure 5 Arachnoid vein showing  $\kappa$  light chain positive tumour cells within the lumen, and smaller extravascular non-stained T lymphocytes (anti- $\kappa$  Dako, original magnification  $\times 100$ ).

cell marker positive tumour cells. These atypical lymphoid cells were also found in renal glomeruli, the pulmonary and coronary vasculature; in fact the only two tissues which seemed unaffected were the lymph nodes and bone marrow. These are the appearances of an intravascular B cell lymphoma.

The diagnostic tests that were performed shortly before the patient's death were nerve and muscle biopsies. Although there was no evidence of intravascular lymphoma from the sural nerve biopsy, the myelinated nerve fibres were considerably reduced in number. The muscle biopsy confirmed atrophy, but this was not necessarily neurogenic in the absence of grouping of the same types of fibre. Within the vessels, however, there were the same CD-20 positive large B cells found elsewhere in the necropsy. In retrospect, detailed examination of the skin biopsy performed 2 months before death also showed occasional intravascular lymphomatous cells, predominantly in the venules.

## Questions

*Professor Charles Warlow*

"What was going on in the spinal roots?"

*Dr Gerard Jansen*

"Exactly the same process. At the lower sacral level in the spinal canal there was an arachnoidal artery with intraluminal tumour cells and surrounding T lymphocytes close to the dorsal root."

*Professor Charles Warlow*

"Were the spinal roots enlarged enough to produce the mass lesion on MR?"

*Dr Gerard Jansen*

"No gross enlargement was present. The vessels were more affected there, but that is all. Presumably the small lesion on MR imaging was an artefact."

*Dr David Bates*

"Why do the lymphoma cells adhere to the endothelium? Do they induce adhesion molecules?"

*Dr Gerard Jansen*

"It is thought that a lack of the CD-18 glycoprotein, which mediates cell to cell adhesion of lymphocytes, may be responsible for the predominantly intravascular location of the lymphoma.<sup>19</sup>"

*Dr Alistair Lammie*

"Are these vessels actually occluded leading to cerebral infarction, or is it perhaps a sludging phenomenon?"

*Dr Gerard Jansen*

"In quite a few instances these blood vessels must become occluded because recanalisation is found. However, partial ischaemia due to sludging cannot be entirely ruled out."

*Dr Geraint Fuller*

"If the lymphoma cells were there on the skin biopsy, were they also there in the liver or bone marrow biopsies?"

*Dr Gerard Jansen*

"There were no abnormal large lymphocytes, but they may have been masked by the abundance of lymphocytes in the liver biopsy due to drug treatment and several blasts in the bone marrow."

*Professor Jan van Gijn*

"The muscle biopsy finally suggested the diagnosis before death, but in retrospect it could have been made on the earlier skin biopsy."

## Professor Charles Warlow's diagnosis

Intravascular lymphoma

## Pathological diagnosis

Intravascular lymphoma



## Comment

There have been fewer than 200 cases of intravascular lymphoma reported after its first description by Pflieger and Tappeiner in 1959.<sup>20</sup> The disease was originally called neoplastic or malignant angioendotheliomatosis and angiotropic large cell lymphoma, but it has been renamed in view of the lymphoid, rather than endothelial, cellular differentiation.<sup>21–22</sup> Intravascular lymphoma is usually high grade and of the B cell phenotype. It has been distinguished from primary CNS lymphoma and Hodgkin's lymphoma by the absence of p53 and bcl-2 proteins.<sup>23</sup> A generalised, monoclonal intravascular expansion of malignant lymphocytic cells causes widespread small vessel occlusion, with occasional extravasation.

Like other non-Hodgkin's lymphomas, intravascular lymphoma has a predilection for middle aged and elderly people, and tends to affect men more often than women. In two thirds of patients the presentation is with neurological disease,<sup>17–18</sup> but it may also include intermittent fever and skin rashes. A review of the literature<sup>18</sup> has identified four main presenting neurological syndromes reflecting the process of vascular occlusion: chronic or subacute encephalopathy, multifocal cerebral infarction, myelopathy, and peripheral or cranial neuropathies. The usual CSF findings of a mild increase in protein and lymphocytic pleocytosis are non-specific, as are increase in plasma lactate dehydrogenase and erythrocyte sedimentation rate. Patients tend to have multifocal cerebral infarction with an affinity for the deep white matter and occasional meningeal enhancement on MR imaging.<sup>24</sup>

Intravascular lymphoma is rarely diagnosed during life<sup>25</sup> as malignant cells are seldom found in the CSF, blood, or bone marrow. Without histological confirmation, its differentiation from other disorders such as vasculitis<sup>26</sup> and isolated angiitis of the CNS<sup>27</sup> can be difficult. Tissue biopsy may be a worthwhile aid to antemortem diagnosis, because survival of over 2 years has been reported after chemotherapy,<sup>28–29</sup> although radiotherapy, steroids, and plasmapheresis do not appear beneficial.<sup>30</sup> The prognosis is otherwise limited to a median of 5 months.<sup>25</sup>

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## Discussants

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- van Gijn J. The Babinski sign: the first hundred years. *J Neurol* 1996;243:675–83.
- Tullous MW, Skerhut HE, Story JL, et al. Cauda equina syndrome of long-standing ankylosing spondylitis. Case report and review of the literature. *J Neurosurg* 1990;73:441–7.
- Lossos A, River Y, Eliakim A, et al. Neurologic aspects of inflammatory bowel disease. *Neurology* 1995;45:416–21.
- Quinn AG, Ellis WR, Burn D, et al. Chorea precipitated by sulphasalazine. *BMJ* 1991;302:1025.
- Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis: diagnosis and management. *Q J Med* 1999;92:103–17.
- Fine HA, Mayer RJ. Primary central nervous system lymphoma. *Ann Intern Med* 1993;119:1093–104.
- Savage CO, Harper L, Adu D. Primary systemic vasculitis. *Lancet* 1997;349:553–8.
- Lie JT. Angiitis of the central nervous system. *Curr Opin Rheumatol* 1991;3:36–45.
- Peat DS, Mathieson PW. Cholesterol emboli may mimic systemic vasculitis. *BMJ* 1996;313:546–7.
- Greaves M. Antiphospholipid antibodies and thrombosis. *Lancet* 1999;353:1348–53.
- Monti G, Galli M, Invernizzi F, et al. Cryoglobulinaemias: a multi-centre study of the early clinical and laboratory manifestations of primary and secondary disease. GISC. Italian Group for the Study of Cryoglobulinaemias. *Q J Med* 1995;88:115–26.
- Serena M, Biscaro R, Moretto G, et al. Peripheral and central nervous system involvement in essential mixed cryoglobulinemia: a case report. *Clin Neuropathol* 1991;10:177–80.
- Reik L Jr, Korn JH. Cryoglobulinemia with encephalopathy: successful treatment by plasma exchange. *Ann Neurol* 1981;10:488–90.
- Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 39–1986. *N Engl J Med* 1986;315:874–85.
- Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 31–1995. A 43-year-old man with multifocal neurologic problems and confusion. *N Engl J Med* 1995;333:992–9.
- Case records of the Massachusetts general hospital. Weekly clinicopathological exercises. Case 30–1996. An 81-year-old man with progressive disorientation, repeated falls, and a fluctuating mental state. *N Engl J Med* 1996;335:952–9.
- Chapin JE, Davis LE, Kornfeld M, et al. Neurologic manifestations of intravascular lymphomatosis. *Acta Neurol Scand* 1995;91:494–9.
- Glass J, Hochberg FH, Miller DC. Intravascular lymphomatosis. A systemic disease with neurologic manifestations. *Cancer* 1993;71:3156–64.
- Jalkanen S, Aho R, Kallajoki M, et al. Lymphocyte homing receptors and adhesion molecules in intravascular malignant lymphomatosis. *Int J Cancer* 1989;44:777–82.
- Pflieger L, Tappeiner J. Zur Kenntnis der systemisierten Endotheliomatose der cutanen Blutgefäße. *Hautarzt* 1959;10:359–63.
- Daniel SE, Rudge P, Scaravilli F. Malignant angioendotheliosis involving the nervous system: support for a lymphoid origin of the neoplastic cells. *J Neurol Neurosurg Psychiatry* 1987;50:1173–7.
- Clark WC, Dohan FC Jr, Moss T, et al. Immunocytochemical evidence of lymphocytic derivation of neoplastic cells in malignant angioendotheliomatosis. *J Neurosurg* 1991;74:757–62.
- Bergmann M, Terzija-Wessel U, Blasius S, et al. Intravascular lymphomatosis of the CNS: clinicopathologic study and search for expression of oncoproteins and Epstein-Barr virus. *Clin Neurol Neurosurg* 1994;96:236–43.
- Williams RL, Meltzer CC, Smirniotopoulos JG, et al. Cerebral MR imaging in intravascular lymphomatosis. *AJNR Am J Neuroradiol* 1998;19:427–31.
- Domizio P, Hall PA, Cotter F, et al. Angiotropic large cell lymphoma (ALCL): morphological, immunohistochemical and genotypic studies with analysis of previous reports. *Hematological Oncology* 1989;7:195–206.
- Walker UA, Herbst EW, Ansoorge O, et al. Intravascular lymphoma simulating vasculitis. *Rheumatol Int* 1994;14:131–3.
- Lie JT. Malignant angioendotheliomatosis (intravascular lymphomatosis) clinically simulating primary angiitis of the central nervous system. *Arthritis Rheum* 1992;35:831–4.
- DiGiuseppe JA, Nelson WG, Seifter EJ, et al. Intravascular lymphomatosis: a clinicopathologic study of 10 cases and assessment of response to chemotherapy. *J Clin Oncol* 1994;12:2573–9.
- Baumann TP, Hurwitz N, Karamitopolou-Diamantis E, et al. Diagnosis and treatment of intravascular lymphomatosis. *Arch Neurol* 2000;57:374–7.
- Williams DB, Lyons MK, Yanagihara T, et al. Cerebral angiotropic large cell lymphoma (neoplastic angioendotheliosis): therapeutic considerations. *J Neurol Sci* 1991;103:16–21.